REMARKS

Under the provisions of 37 C.F.R. 1.136(a), submitted herewith is a Petition for a Three-Month Extension of Time extending the period for response to the instant Office Action to June 19, 2001. This amendment is therefore timely filed.

Claims 1-43 were in the application as filed. Restriction has been required among nine groups of claims as follows:

Group I, claims 1-4, 37 and 39-43, drawn to a polypeptide comprising SEQ ID NO: 2.

Group II, claims 5-7, 14-17, 25, 29 and 30, drawn to a nucleic acid comprising SEQ ID NO: 1.

Group III, claims 8-10, 37, 39-43, drawn to a polypeptide comprising SEQ ID NO: 4.

Group IV, claims 11-17, 25, 29 and 30, drawn to a nucleic acid comprising SEQ ID NO: 3.

Group V, claim 24, drawn to an antisense molecule.

Group VI, claims 18-20 and 26-28, drawn to a probe targeted to a nucleic acid comprising SEQ ID NO: 1.

Group VII, claims 21-23 and 26-28, drawn to a probe targeted to a nucleic acid comprising SEQ ID NO: 3.

Group VIII, claims 31-34, drawn to an antibody.

Group IX, claims 35 and 36, drawn to a modulator and a method of identifying said modulator.

The restriction requirement is respectfully traversed and reconsideration thereof is requested. The claims are directed to polypeptides having IL-13 receptor activity, to nucleic acid sequences encoding them and to various uses thereof. Thus the claims are drawn to different aspects of a common inventive concept and should be examined together. Nevertheless, in order that this response be complete, applicants hereby affirm the provisional election of Examiner's Group I, claims 1-4, 37 and 39-43 drawn to a polypeptide comprising SEQ ID NO: 2, made by applicants' undersigned

representative in a telephone conversation with Examiner Karen Lacourciere on September 1, 2000. Accordingly, claims 5-36 and 38 stand withdrawn from consideration as drawn to non-elected subject matter and claims 1-4, 37 and 39-43 are under examination. Claims 1-4, 37 and 39-43 are canceled without prejudice to the prosecution thereof in a continuing application and new claims 44-59 are added. No new matter is added by the present amendment.

The specification is objected to as not containing an abstract, a title and a brief description of the drawings. Applicants point out that the specification does in fact contain an abstract and title of the invention on a separate page immediately following the last page of the claims (page 49). Receipt of the abstract in the PTO is evidenced by a stamped postal receipt card. A copy of the abstract page and the postal receipt card are submitted herewith. The specification also contains a brief description of each of the drawings in the section entitled LEGEND TO THE FIGURES (pages 13-16). Pursuant to the instant amendment the title is amended to read "BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS" and the drawing descriptions are amended to correspond to the drawings as amended herein.

The drawings are objected to as being improperly labeled. The objection is believed overcome by the instant amendment wherein the views of Figures 1, 2, 4, 7 and 8 are labeled in accordance with 37 C.F.R. 1.84 (m)(1).

Lastly, regarding the specification, the sequence WSXWS disclosed at page 24, line 11 is objected to as lacking reference to a SEQ ID NO:. The objection is believed overcome by the instant amendment wherein the paragraph beginning at page 24, line 6 is rewritten to include reference to "SEQ ID NO: 13" for the sequence WSXWS.

Claims 1-4 are objected to because the sequence identifiers are referred to as "SEQ ID No." rather than "SEQ ID NO:", and claim 3 is objected to as lacking reference to a SEQ ID NO. for the sequence VRCVTL. These objections are rendered moot by the cancellation of claims 1-4.

Claims 37, 40, 42 and 43 are objected to as being in improper dependent form. The objection is rendered moot by the cancellation of said claims.

Claims 39-43 are rejected under 35 U.S.C. 101 as directed to non-statutory subject matter. The rejection is rendered moot by the cancellation of said claims.

Claims 1-4, 37 and 39-43 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. The rejection is rendered moot by the cancellation of said claims.

Claims 1, 3, 4, 37 and 39-43 are rejected under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, as not supported by either a specific and substantial asserted utility or a well established utility. The rejection is moot in view of the cancellation of said claims.

Claims 37 and 42 are rejected based on the failure of the specification to enable one of skill in the art to make and/or use the pharmaceutical composition encompassed by the claim. Cancellation of claims 37 and 42 renders the rejection moot.

Claims 1, 3, 4, 37 and 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention. The rejection is moot in view of the cancellation of said claims.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Sigma and claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Vita et al. The rejections are rendered moot by the cancellation of claims 1 and 2.

New claim 44 corresponds to original claim 1 wherein the "biologically active sequence derived from SEQ ID NO: 2" is more particularly described as SEQ ID NO: 2 in which the 8 c-terminal residues are substituted by VRCVTL (SEQ ID NO: 11), or a soluble sequence of residue 1 to 337 or 1 to 343 of SEQ ID NO: 2. New claims 45, 46 and 47 correspond to original claims 2, 3 and 4 respectively. New claims 48-51 correspond to original multiply dependent claim 37 written in singly dependent form and limited to the elected subject matter. Likewise, new claims 52-55 correspond to original multiply dependent claim 39 written in singly dependent form, and new claims 56-59 correspond to original multiply dependent claim 41 written in singly dependent form.

New claims 44-59 are believed to obviate all objections and rejections made with respect to original claims 1-4, 37 and 39-43. Thus, in new claims 44-47, all

sequences are identified by the appropriate SEQ ID NO: in the format prescribed by 37 C.F.R. 1.821.

None of dependent claims 45-59 depends from a non-elected claim.

Claims 52-59 are directed to screening and treatment methods and thus are proper process claims under 35 U.S.C. 101 and 35 U.S.C. 112, second paragraph.

The language that gave rise to the rejection of original claims 1-4 and 39-43 under 35 U.S.C. 112, second paragraph, as being indefinite, i.e. "any biologically active sequence derived from SEQ ID NO: 2" (claim 1), "variant" (claim 3), "preferably up to" (claims 1 and 4), "stretching up to" (claim 4), "activity" (claims 39-42), is not present in new claims 44-59.

New claims 44-59 also obviate the various rejections of original claims 1, 3, 4, 37 and 39-43 under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, as not supported by a specific and substantial utility; as not enabling use of the invention commensurate in scope with the claims without undue experimentation, and as claiming subject matter not adequately described in the specification.

Thus, claim 44 is directed to a specific and well defined group of polypeptides which are clearly and fully described in the specification. The specification also teaches how to make said polypeptides and describes the use thereof in a screening method for agonists or antagonists of IL-13, a known mediator of immunological and inflammatory mechanisms, and as agents for treating such IL-13-mediated conditions. (P. 4, lines 12-32; p. 12, line 31; p. 13, line 28). As described at page 12, line 13 – page 13, line 4, test compounds are brought into contact with a polypeptide of the invention and the binding of test compound to polypeptide is measured. Alternatively, IL-13 may be brought into contact with the polypeptide, and its binding in the presence or absence of a test compound is measured to determine the inhibition of IL-13 binding by the test compound. This is a classic competitive binding experiment well known in the art and requires no undue experimentation. In this way, the inhibition of the binding of IL-13 to cell surface receptors by the claimed polypeptides in soluble form was determined (Example 6 and FIG. 5 and 6). These experiments demonstrate that the claimed polypeptides are also useful in blocking the activity of IL-13. As noted by applicants, IL-13 is a mediator of inflammatory mechanisms (p. 4, lines 15-16), and as confirmed in the

research publication by Wills-Karp et al., in Science 282, (5397), 2258 (copy submitted herewith), blockade of IL-13 was effective in reversing allergen-induced asthma. Clearly then, the use of the instant polypeptides to screen for IL-13 antagonists as well as the use thereof in pharmaceutical compositions for blocking IL-13 represent specific and substantial real world utilities.

Lastly, it is pointed out that the purified polypeptides here-claimed are neither taught nor suggested by the prior art, in particular the Sigma Catalog and Vita et al. (J. Biol. Chem. 270, 3512 (1995)) cited by the Examiner.

It is therefore submitted that the subject matter of claims 44-59 is novel and unobvious; is clearly useful; is fully and unambiguously described in the specification so as to enable one skilled in the art to make and use it without undue experimentation, and hence that claims 44-59 are patentable and should be allowed.

It is believed that a discussion of the foregoing would be useful in expediting the proceedings in this case and accordingly applicants' undersigned representative invites the Examiner to contact him by telephone after having had an opportunity to study this response.

Attached hereto is a page entitled "Version With Markings To Show Changes Made" which shows the changes made to the specification and claims by the instant amendment.

Respectfully submitted,

Dated: June 19 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The section entitled "LEGEND TO THE FIGURES" beginning at page 13, line 33 has been amended as follows.

BRIEF DESCRIPTION OF THE DRAWINGS

- Figure 1: characterization of the human IL-13Rß receptor present in Caki-1 cells.

[a)] FIG. 1A Scatchard analysis (inset) of the saturation curve of IL-13 labelled with [^{125}I];

[b)] FIG. 1B binding of [^{125}I][Phe43]-IL-13-GlyTyrGlyTyr in the presence of increasing concentrations of unlabelled IL-13 (·) and of IL-4 (o);

[c)] FIG. 1C cross-linking experiments using radioactive IL-13 in the absence (lane a) and in the presence of a one hundred times excess of unlabelled IL-13 (lane b) or of IL-4 (lane c);

[d)] FIG. 1D inhibition of the secretion of IL-6 induced by IL-13 and IL-4 in the presence of a monoclonal antibody specific for the IL-4R chain and the IL-4 antagonist Y124DIL-4.

- Figure 2: Nucleotide sequence of the cDNA of IL-13Rß (SEQ ID NO. 1), and comparison of the protein sequences of IL-5R (SEQ ID NO. 5) and IL-13Rß (SEQ ID NO. 2).

[a)] FIG. 2A & 2B nucleotide sequence of the cDNA of IL-13Rß (SEQ ID NO. 1). The amino acids corresponding to the deduced signal peptide of the nucleic sequence are indicated in italics and those corresponding to the transmembrane domain are indicated in bold characters. The potential N-glycosylation sites (Asn-X-Ser/Thr) are underlined;

[b)] FIG. 2C alignment of the amino acids of the IL-13Rß (SEQ ID NO. 2) and IL-5R (SEQ ID NO. 5) sequences. The protein sequences of IL-13R (SEQ ID NO. 2) and IL-5R

(SEQ ID NO. 5) are aligned as described above (24). The cysteine residues and the WSXWS (SEQ ID NO. 13) motif which are characteristic of this family of receptors are boxed.

- [Figure] FIG. 3: patterns of expression of the IL-13Rß mRNA.
The RNA was prepared from the following cells: Caki-1 (lane a), A431 (lane b), TF-1 (lane c), U937 (lane d), Jurkat (line e) and IM9 (lane f).

- Figure 4: characterization of the recombinant IL-13Rß receptor for IL-13. The COS-7 cells are transfected with IL-13Rß cDNA and used for:

[a)] FIG. 4A studies for the binding of radiolabelled IL-13 (inset) by Scatchard analysis of the saturation curve;

[b)] FIG. 4B cross-linking experiments using radiolabelled IL-13 in the absence (lane a) and in the presence of a one hundred times excess of unlabelled IL-13 (lane b);

[c-d)] FIG. 4C & 4D cotransfection experiments using cloned IL-13Rß, IL-4R (gp140) and the γc chain followed by the binding of radiolabelled IL-13 (c) or of IL-4 (d). The black and white columns represent the specific binding of IL-13 and of IL-4 respectively.

- [Figure] FIG. 5: inhibition of the binding of IL-13 to IL-13Rß by the soluble form of the receptor (IL-13Rßs) in transient expression.
The expression of IL-13Rßs in the supernatant of the cells transfected with 2034 is tested by inhibition of the binding of IL-13 on cells transfected with IL-13Rß (2036). The supernatants are tested in the crude state by diluting them one half in the iodinated ligand.
2036 NSB: nonspecific binding in the presence of an excess of unlabelled IL-13.
2036 BT: total binding on cells transfected with 2036
2036 + sgt 2034: binding to cells transfected with 2036 in the presence of supernatant of cells transfected with 2034.
2036 + sgt pSE1 : control

- [Figure] FIG. 6: inhibition of the binding of IL-13 to IL-13Rß by the soluble form of the receptor (IL-13Rßs) on stable lines.
T2036-22: total binding on the clone IL-13Rß (2036-22) in the absence of supernatant of clone secreting IL-13Rßs (reference 100%)
2034-4

2034-6
2034-19 4 clones IL-13Rß s
2034-21
1274-20: in the presence of supernatant of CHO cells not expressing IL-13Rßs (control).

- Figure 7: nucleotide sequence of the IL-13Rß (SEQ. ID NO. 3) cDNA and comparison of the protein sequences of human IL-13Rß (SEQ. ID NO. 4) and of murine IL-13Rß (SEQ. ID NO. 6).

[a)] FIG. 7A & 7B Nucleotide sequence of the IL-13Rß (SEQ. ID NO. 3) cDNA. The amino acids corresponding to the signal peptide deduced from the nucleic sequence are underlined with a dotted line and those corresponding to the transmembrane domain are underlined with a double line. The potential N-glycosylation sites (Asn-X-Ser/Thr) are boxed.

[b)] FIG. 7C & 7D Alignment of the amino acids of human IL-13Rß (SEQ. ID NO. 4) and of murine IL-13Rß (SEQ. ID NO. 6). The protein sequences of human IL-13Rß (SEQ. ID NO. 4) and of murine IL-13Rß (SEQ. ID NO. 6) are aligned as described above (24). The cysteine residues and the motif WSXWS (SEQ. ID NO. 3) which are characteristic of this family of receptors are boxed.

- Figure 8: characterization of the recombinant IL-13Rß receptor for IL-13.
The CHO or COS-3 cells transfected with the IL-13Rß and/or IL-4R cDNA and used for:

[a)] FIG. 8A & 8B studies of the binding of iodine-125 labelled IL-13 by Scatchard analysis of the saturation curve with CHO cells transfected with IL-13Rß cDNA ([Figure] A), transfected with IL-13Rß cDNA and IL-4R cDNA ([Figure] B), transfected with IL-13Rß cDNA ([Figure] C) and transfected with IL-13Rß cDNA and IL-4R cDNA ([Figure] D),

[b)] FIG. 8A & 8B competition experiments of binding of [^{125}I]-IL-13 on CHO cells transfected with IL-13Rß cDNA ([Figure] E), transfected with IL-13Rß cDNA and IL-4R cDNA ([Figure] F), transfected with IL-13Rß cDNA ([Figure] G) and transfected with IL-13Rß cDNA and IL-4R cDNA ([Figure] H). The white and shaded columns represent respectively the specific binding of radiolabelled IL-13 in the presence of an excess (1,000 times more) of IL-13 or IL-4, the black columns represent total binding.

- [Figure] FIG. 9: comparison of the electrophoretic mobility in EMSA of cellular extracts expressing the receptor for IL-4 alone (CHO-4), the receptor for IL-13Rß alone (CHO-13) or the combined receptors IL-13Rß and IL-4R (CHO-4-13) after activation of the CHO cells in the presence of IL-4 or IL-13 (4 or 13), c representing the nonactivated control.

The paragraph beginning at page 24, line 6 has been amended as follows.

Four potential N-glycosylation sites are located in the extracelluar region. It is important to note that two consensus motifs considered as signatures of the type II family of cytokine receptors (30) are also present, the first being derived from an N-terminal disulphide bridge loop structure, the second being the WSXWS (SEQ. ID NO. 13) type motif located at the C-terminal end of the extracellular region. The very short cytoplasmic sequence might explain why it is only the receptor complex shared by IL-4 and by IL-13 in the Caki cells which transduces a signal in the cell.

Figures 1, 2, 4, 7 and 8 have been amended as indicated in red on the sheets submitted herewith.

In the Claims:

Claims 1-4, 37 and 39-43 have been cancelled.

New claims 44-59 have been added.